

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202860Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 202860
GeNOsyl DS®-Delivered Nitric Oxide for
Inhalation

Integrated Quality Review
(2nd Resubmission; Resub-45)

Recommendation: Approval

Drug Product	GeNOsyl (nitric oxide) for inhalation
Product (Nitric Oxide) Delivery System Device	GeNOsyl Delivery System® (GeNOsyl DS®)
Maximum Drug Dose Delivered to the Patient	20-ppm
Route of Administration	Inhalation of nitric oxide gas (mixed with air or O2)
Rx/OTC Dispensed	Rx
Applicant	Vero Biotech, LLC (formerly known as GeNO, LLC)
Submissions (s) Reviewed	NDA 202860-Resub-45, and all the submitted CMC amendments

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance and Drug Product	Charles Jewell	ONDP/DNDAPI/NDBI
Process & Facility	Laurie Nelson	OPQ/OPF/DIA/IABI
Device Component	Neel Patel	CDRH/ODE/DAGID/ANDB
Regulatory Business Process Manager	Grafton Adams	OPRO DRBPMI/RBPMBI
Application Technical Lead (ATL)	Mohan Sapru	ONDP/DNDPI/NDPBI

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 202860 resubmission (GeNOsyl DS®-Delivered Nitric Oxide for Inhalation) is recommended for approval.

B. Recommendation on Post-Marketing Commitments (PMCs), Agreements, and/or Risk Management Steps, if Applicable

Not applicable.

II. Background

The applicant submitted the original NDA 202860 for GeNOsyl™ MVG 2000 Delivery System for inhaled nitric oxide (NO) on March 20, 2012. The applicant (GeNO, LLC) received a Refusal to File letter from the Agency on May 18, 2012. GeNO, LLC resubmitted the NDA on August 31, 2012. Because of several unresolved drug-device and manufacturing-related deficiencies, a Complete Response Letter was issued on June 28, 2013. Per NDA 202860 Class 2 resubmission dated July 23, 2018, the applicant Vero Biotech (formerly known as GeNO, LLC), sought U.S. marketing approval for the drug-device combination product, GeNOsyl Delivery System® (GēNOsyl DS®), which involved significant improvements in device design. On January 23, 2019, the Agency issued a Complete Response Letter because of unresolved deficiencies regarding the: a) manufacturing facilities, b) device, and c) human factor studies (for details, please refer to Complete Response Letter, DARRTS, 01/23/2019). On June 21, 2019, the applicant (Vero Biotech LLC) sought U.S. marketing approval for the drug-device combination product, GēNOsyl (b) (4), in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act by resubmitting NDA 202860 (Class 2 NDA 202860-Resub-45) for the treatment of persistent pulmonary hypertension of the newborn. The Agency granted orphan-drug designation for this indication under Orphan Designation 12-3685. The Listed Drug (LD) for this resubmitted NDA is INOmax® (nitric oxide for inhalation) approved under NDA 020845. To support this application, Vero Biotech is relying on: a) information in the approved labeling for INOmax® regarding the safety and efficacy of inhaled nitric oxide, b) clinical studies (in adults) conducted by Vero Biotech, c) (b) (4); and d) information in the public domain (i.e., published clinical studies on the safety and efficacy of inhaled nitric oxide).

III. Overall Assessment Summary

- The originally proposed drug-device combination product for inhaled nitric oxide i.e., the GeNOsyl MVG 2000 Delivery System has undergone significant design changes since the original NDA submission. The proposed GeNOsyl Delivery System® (GeNOsyl DS®), a liquid-based delivery system for inhaled nitric oxide (NO), represents a significantly improved system with marked design changes aimed to consistently deliver well-controlled levels of nitric oxide to the patients while restricting nitrogen dioxide (NO₂) levels within the safe limits. To avoid any unsupported promotional claim, the applicant has

been recommended to refer to the proposed drug-device combination product as GeNOsyl Delivery System® (GeNOsyl DS®).

- **Assessment of Manufacturing Facilities:** The listed manufacturing site i.e., Vero Biotech facility (FEI: 3014617112) performs cassette and drug constituent part of manufacturing, packaging, release and stability testing. Based on the risk assessment, this facility was deemed 'high risk' due to: a) the facility was previously found to be not ready for commercial manufacturing, b) high risk API (b) (4) (b) (4) c) product and device complexity (combination product designation). The facility was re-inspected and the Office of Pharmaceutical Manufacturing Assessment (OPMA) assessor participated in the inspection. Based on the reinspection outcome and the overall compliance of the facility, OPMA has issued "approved" recommendation for the facility. In addition, a follow-up of preapproval inspection (PAI) was conducted for (b) (4) facility, which performs (b) (4) manufacturing. Based on inspection report, discussion with the district office, review of the 483 observations, the firm's responses and the CDRH consultation, the facility is deemed "approved".
- Based on PAI of manufacturing facilities, and risk and science-based evaluation of product quality and the device (GeNOsyl DS®), including the human factor studies, the applicant, in the current Class 2 resubmission, has adequately addressed the deficiencies listed in the Agency's Complete Response Letter of January 23, 2019. For detailed evaluation of the device and human factor studies, please refer to CDRH and DMEPA reviews (DARRTS 12/17/2019 and DARRTS 11/14/2019), respectively. Salient review details about the proposed product i.e., Genosyl (nitric oxide) for inhalation and nitric oxide delivery system (device) are listed below.

IV. Drug-Device Combination Product (GeNOsyl DS®)

A. Nitric Oxide Delivery System (Device):

- GeNOsyl DS® generates and delivers nitric oxide for inhalation at the point-of-use. The concentration of nitric oxide, as set by the user, is monitored and adjusted to accurately dose the patient throughout an inspired breath.
- The main components of the GeNOsyl DS® are:

Consoles: There are two consoles i.e., the primary console and the standby (redundant) console. The consoles convert dinitrogen tetroxide/nitrogen dioxide (N₂O₄/NO₂) liquid into nitric oxide gas. The redundant console is for complete backup capability for delivery of nitric oxide for inhalation. Each Console has a back-up battery that provides up to one hour of nitric oxide delivery in the absence of an external power source.

Cassette: One cassette is inserted into each Genosyl (b) (4) Console. The cassettes contain the liquid N₂O₄/NO₂ (b) (4) the antioxidant cartridges and the inerting material. Both consoles and associated equipment are mounted on a mobile cart.

- The nitric concentration (dose) to be delivered to the patient is selected by the user, set and maintained independently by means of computer-controlled air pumps, cassette heaters, and a feedback loop that measures the delivered nitric oxide concentration. Specifically, the console provides the nitric oxide delivery controls in addition to safety controls. The delivered nitric oxide concentration is regulated by the liquid vessel temperature and the console internal flow controls.

- The GeNOsyl DS® console contains the electronics to control the production and to maintain the constant and precise delivery of nitric oxide. Prior to reaching the patient, the gas passes through an inline mixing chamber, which is used to ensure a uniform intrabreath nitric oxide dose.

B. Drug Substance Quality Summary

Nitric oxide (NO) drug substance, a colorless and odorless gas, is generated at the point-of-use within the GeNOsyl DS®. The drug substance has been well-characterized using appropriate analytical tools such as mass spectrometry, (b) (4). Nitric oxide drug substance quality is controlled by adequate in-process controls and release specifications (b) (4).

i. The identity, quality and purity of each batch of N₂O₄ and antioxidant cartridges are assessed and confirmed according to the specifications using validated analytical procedures. Nitrogen dioxide (NO₂) is the only potential related impurity observed and monitored. An antioxidant cartridge is approximately 3.7 inches long with an outside diameter of 1.5 inches and an internal diameter of 0.25 inches with a tapered end. The cartridge (b) (4)

antioxidant cartridge release specification with well-justified acceptable limits of less than 2 ppm, which is within the safe limits for NO₂. The GeNOsyl DS® system shutdown condition for NO₂ is 3 ppm. The NO₂ output above 2 ppm during the timeframe of the test indicates a cartridge NO₂ conversion performance failure. Based on stability data, a (b) (4) retest period is acceptable for the N₂O₄ (b) (4)

(b) (4) the current level of understanding is adequate to support the use of the cartridges as per the proposed specification for up to 12 months from their time of manufacture. The applicant has proposed the breakthrough testing (i.e., demonstration that the cassette excess capacity to convert the maximum level of NO₂ produced (b) (4) of N₂O₄ into NO) as the stability-indicating method of choice. This approach is acceptable.

C. Drug Product Quality Summary

The drug product is composed of (b) (4) ppm to 800 ppm nitric oxide (NO) in (b) (4) room air to be delivered at a recommended maximum dose concentration of 20 ppm to the patient to reduce the need for extracorporeal membrane oxygenation in near-term (>34 weeks gestation) or full-term neonates. There are no excipients added to the nitric oxide (b) (4) drug product. The drug product cassette contains all components and material necessary to safely generate nitric oxide (NO) for inhalation. The finished nitric oxide drug product quality is controlled by adequate in-process manufacturing controls and quality control specifications using validated analytical procedures. All specifications for cassette testing are adequately justified. Validation information demonstrating that the analytical procedures used to test drug product are suitable for their intended purpose is adequate. The cassette is demonstrated to (b) (4) the capacity to convert maximum contained N₂O₄ into nitric oxide while maintaining the NO₂ levels below 2 ppm. A critical aspect of the design is that if functional defect is detected by

the console during operation, there is a backup system in standby state, which is ready to provide nearly continuous nitric oxide supply with minimal interruption. The production of quality drug product has been verified by testing and comparison to acceptable reference standards. From analytical perspective, the (b) (4) sensor is specific for nitric oxide. (b) (4) methodology for detection of NO₂ is highly sensitive and specific even in the presence of significant levels of nitric oxide. The proposed (b) (4) which is a simulated version of the commercial console under conditions that simulate proposed use is acceptable. Based on data provided, the cassettes can typically provide nitric oxide at 20-ppm for a period (b) (4) without breakthrough NO₂ when the standard 20-ppm nitric oxide settings are in place. Various product development studies conducted by the applicant have shown that; a) NO₂ conversion to nitric oxide from liquid N₂O₄ and from a calibrated cylinder produce chemically identical nitric oxide, and b) the GeNOsyl DS®, using a liquid N₂O₄ source material, can deliver nitric oxide gas at a controlled target dose level. The product release specification includes testing for levels of NO₂ output with an acceptance limit of 2 ppm. Based on testing and risk assessment of product elemental impurities per ICH Q3D, the elemental impurity levels are below the control threshold (30% of the PDE) and no additional controls are necessary.

D. Manufacturing: The GeNOsyl DS® operates by producing nitric oxide from N₂O₄ liquid, which is stored in a nitric oxide drug product cassette containing two antioxidant cartridges. (b) (4)
(b) (4)



E. Container-Closure System: The proposed container closure system for the drug product cassette houses the subcomponents necessary for the generation of nitric oxide drug product. Based on appropriate testing, the applicant has demonstrated the adequacy of the proposed container closure system, including the primary and secondary packaging for the cassette.

F. Biocompatibility: The device components evaluated for biocompatibility are part of the gas pathway, which delivers a constant intra-breath concentration of therapeutic nitric oxide to patients who are on a ventilator. No part of the device or supplied accessory components makes direct contact with the patient during use. The patient gas flow path includes flow through the cassette, console, and supplied ventilator circuit accessories. Leachable and extractable gas pathway material characterization performed on all GeNOsyl DS® gas pathway component materials are adequate. A gas pathway evaluation for nitric oxide within the cassette and console has been carried out in accordance with ISO (b) (4) for emissions of Volatile Organic Compounds (VOCs) and particulate matter. Specifically, the risk assessment has focused on volatile compounds and particulates that may be released into the gas pathway of the GeNOsyl DS® and, therefore, subject to inhalation by a patient. The VOCs identified in the gas pathway analysis, expressed as estimated daily intake, have been found to be at levels below the established Toxicological Threshold of Concern (TTC). The particulate matter levels have not exceeded the allowable limits. Although no VOC exceeded a TTC (per ISO (b) (4) guidance), (b) (4) have been subjected to a more in-depth assessment because of the well-known toxicity limits for these chemicals. The potential levels of exposure for both (b) (4) have been demonstrated to be below toxicological thresholds of concern.

G. Stability, and Expiration Date:

(b) (4)

Thus, the proposed expiration dating period of 12 months, marked based on the manufacturing date of the oldest cartridge used to assemble the cassette, is granted.

V. Drug-Device Combination Product (GeNOsyl DS®) Benefit-Risk Integrated Assessment

Regarding (GeNOsyl DS®), the major potential risk factors evaluated using science and risk-based approach include: a) the possibility of hazardous exposure to poisonous dinitrogen tetroxide (N₂O₄) or NO₂, b) controls

for generation of nitric oxide and c) device-related controls for safe use of the proposed drug-device combination product. It is noted that these potential risks factors have been adequately addressed based on the following device features and validated controls for product generation and delivery:

- The proposed GeNOsyl DS® is a liquid-based delivery system for inhaled nitric oxide.
- In response to Agency's two Complete Response Letters and identified deficiencies, the GeNOsyl DS® has undergone significant design changes from the time of original NDA submission.
- The product (nitric oxide) manufacturing involves (b) (4)
(b) (4)
Specifically, upon initiation of the system, the liquid N₂O₄ is heated and the equilibrium shifts to NO₂ (gas). The NO₂ is then converted into nitric oxide using the antioxidant cartridges, and nitric oxide is delivered to the patient by means of a ventilator or a nasal cannula.
- The amount of nitric oxide administered to the patient is set by controlling the temperature of the N₂O₄ liquid module, which controls the pressure inside the liquid module, which in turn controls the mass of NO₂ that is sent to the primary cartridges, and hence the mass of nitric oxide.
- The GeNOsyl DS® system shutdown condition for NO₂ is 3 ppm
- N₂O₄ (b) (4) are tested for stability (b) (4) at elevated temperatures. In the GeNOsyl DS®, the (b) (4) is installed into a metal cylinder with a tiny capillary output tube. On activation, the N₂O₄ is distilled out as NO₂ gas by carefully controlled heating of the metal chamber and the capillary pathway
- In the event NO₂ levels reach 3-ppm or above, the console shuts down and signals activation of the backup cassette. When an activated cassette is shut down for nitric oxide production, all NO₂ and any potential N₂O₄ release is quenched by the internal quenching pathway, preventing escape to the external environment
- Regarding risk assessment of exposure of patients, the liquid vessel is surrounded by inserting chamber with absorbing inerting material, which absorbs and neutralizes NO₂/N₂O₄ that leaves the liquid vessel before, during and after use.
- Amount of inerting material required (b) (4) of N₂O₄ is (b) (4) grams. There is (b) (4)-times that amount contained in the inerting chamber.
- Because of the total quantity of N₂O₄ (b) (4) gas release into a room does not pose a risk.
- CDRH device review team concluded that the device does not need additional capability and controls beyond nitric oxide and NO₂ controls incorporated into the current device design.
- Based on human factor studies, there are no identified use related risks associated with accidental release of N₂O₄ during use (including set-up, administration, changing cartridges, (b) (4) etc.) or storage of the system.
- The applicant has provided a hazard analysis that includes accidental user and patient exposure to N₂O₄ due to mechanical failure. Based on the device review by CDRH, the risks of exposure are acceptably mitigated through the design of the cassette and amount of N₂O₄ present and that N₂O₄ will not reach the console/delivery system. The FMEA provided for the cassette and console address accidental NO₂ exposure including (b) (4) material/cartridge for gas exiting the cassette. High NO₂ alarms (adjustable from 1 to 2 ppm) and the shutdown capability if NO₂ at greater than 3-ppm level in the delivered gas are adequate.
- The GeNOsyl DS® system provides continuous integrated monitoring of inspired oxygen, NO and nitrogen dioxide (NO₂) concentrations, and a comprehensive alarm system.
- The GeNOsyl DS® is intended for use by healthcare professionals who are licensed and actively practicing pediatric and/or neonatal respiratory therapists (RTs) in the United States. These users are required to set up, administer inhaled nitric oxide and provide respiratory care.
- INOmax (nitric oxide) is a gas available in an 800-ppm concentration. The recommended delivered dose of NO using INOmax is 20-ppm. Active pharmaceutical Ingredient in both the proposed product and

listed drug INOmax is nitric acid. The GeNOsyl DS® also generates up to 800-ppm nitric oxide and delivers the same dose strength of nitric oxide as the currently approved listed drug INOmax (i.e., 20-ppm).

VI. Environmental Assessment

The applicant's requests for a categorical exclusion pursuant to 21 CFR 25.15(d) and 21 CFR 25.20 as described under 21 CFR 25.31(a) is acceptable.

VII. Label and Labeling

All recommendations have been incorporated by the applicant in the most recent version of the label and labeling.

VIII. Life Cycle Knowledge Management/Final Risk Assessment

Pleased view the following page:

Final Risk Assessment
NDA 202860 Resubmission (GeNOsyl (b) (4))

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors Affecting CQA	Initial Risk Ranking	Risk Mitigation	Final Risk Evalu	Life Cycle Managem ent Comment
Nitrogen Dioxide (NO ₂) Output (Impurity Content)	Manufacturing Controls Process Parameters Device Controls Cartridge Performance	H (High)	The product release specification includes testing for levels of NO ₂ output with an acceptance limit of < 2 ppm, which is within the permitted safety limits for this poisonous gas. The GeNOsyl DS® system shutdown condition for NO ₂ is 3 ppm.	Acceptable	Any change in drug product release specification and/or changes in cartridges design needs to be carefully examined to ensure that final NO ₂ output levels are maintained at < 2 ppm.
Assay (API), Product Stability	Formulation Container Closure Process Parameters Device components	M (Moderate)	Based on the stability data, the proposed expiration dating of 12 months for the GeNOsyl (b) (4) drug product cassette is acceptable.	Acceptable	Stability of the cartridge is not well defined, though demonstrated to be acceptable for 12 months from date of manufacture of the cartridge, including the assurance that a redundant (i.e., second cartridge) is maintained in the cassette, so that more than double the capacity to convert all the NO ₂ gas produced from the N ₂ O ₄ (b) (4) cassette. Any increase in stability periods for the cassette may need to be carefully evaluated.

Manufacturing Controls	Process Parameters In-Process Controls Product Device Functional Integration Manufacturing Practices cGMP Device Testing	H (High)	The product quality seems to be well controlled based on proposed manufacturing in-process controls and release specifications. Based on pre-approval inspections, all the manufacturing facilities are deemed “approved”.	Acceptable	Satisfactory resolution of Form 483-listed deficiencies is required.
Leak Test Pouch Seal Integrity	Cartridge Pressure (b) (4) Specification Container Closure Integrity	M (Moderate)	Controls for cassette assembly include adequate in-process controls such as (b) (4) (b) (4) Pouch seal integrity integrity test are adequate.	Acceptable	

Final Risk Assessment (continued)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors Affecting CQA	Initial Risk Ranking	Risk Mitigation	Final Risk Evaluation	Comments
Compatibility	Formulation Raw materials Process parameters Container Closure	L (Low)	Compatibility test studies are adequate.	Acceptable	
Uniformity of Delivered Dose Under Conditions of Use	Manufacturing Chemistry Console Performance Cartridge Performance Device Controls	H (High)	Adequately ensured by the proposed drug-device product	Acceptable	All future modifications should be assessed while being mindful of the criticality of the cartridge design,

Particulate Matter	Formulation Container Closure Process Parameters Device controls	L (Low)	The particulate matter levels have not exceeded the allowable limits.	Acceptable	
Leachable Extracts	Container Closure Folds Creases, Tears	L (Low)	Leachable and extractable gas pathway material characterization performed on all GeNOsyl ^{(b) (4)} gas pathway component materials are adequate.	Acceptable	
Monitoring of NO, NO2	Drug-Device Controls	H (High)	The system has continuous monitoring by electrochemical NO, NO2, and O2 sensors during use.	Acceptable	Any drug-device design changes will require careful evaluation to ensure continuous monitoring of NO, NO2, and O2

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead (ATL) Assessment and Signature:

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 202860 resubmission (GeNOsyl DS®-Delivered Nitric Oxide for Inhalation) is recommended for approval.

Mohan Sapru, M.S., Ph.D.
Application Technical Lead (ATL)
CMC Lead for Cardiovascular and Renal Products
ONDP/DNDPI/NDPBI

Mohan K. Sapru -S
 Digitally signed by Mohan K. Sapru -S
 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mohan K. Sapru -S, 0.9.2342.19200300.100.1.1=2000589315
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**NDA 202860 GēNOsyl ^{(b) (4)} Resubmission
(Drug-Device Combination Product)**

Integrated Quality Review

Recommendation: A Complete Response (CR)

Drug-Device Combination Product Name	GēNOsyl ^{(b) (4)} Delivery System [®] (GēNOsyl ^{(b) (4)})
Drug Product	Nitric Oxide (NO) ^{(b) (4)}
Maximum Drug Dose to be Delivered to the Patient	20 ppm
Route of Administration	Inhaled NO gas (uniform intra-breath NO dose).
Rx/OTC Dispensed	Rx
Applicant	Vero Biotech, LLC (formerly known as GeNO, LLC)
Submissions (s) Reviewed	NDA 202860 Resubmission, and all the Submitted CMC Amendments

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance and Drug Product	Charles Jewell	ONDP/DNDAPI/NDBI
Process & Facility	Steven Hertz	OPQ/OPF/DIA/IABI
Device Component	Neel Patel	CDRH/ODE/DAGID/ANDB
Regulatory Business Process Manager	Grafton Adams	OPRO DRBPMI/RBPMBI
Application Technical Lead (ATL)	Mohan Sapru	ONDP/DNDPI/NDPBI

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 202860 resubmission (GēNOsyl (b) (4)) is not recommended for approval because the Office of Process and Facilities has issued a “Withhold” recommendation for Vero Biotech manufacturing facility (FEI: 3014617112). Satisfactory resolution of all the Form 483-listed deficiencies concerning this facility is required before this NDA is considered for approval.

B. Recommendation on Post-Marketing Commitments (PMCs), Agreements, and/or Risk Management Steps, if Applicable

Not applicable.

II. Background

The applicant submitted the original NDA 202860 for GeNOsyl™ MVG 2000 Delivery System for inhaled nitric oxide (NO) on March 20, 2012. Due to several unresolved drug-device and manufacturing-related deficiencies, a Complete Response Letter was issued for NDA 202860 on June 28, 2013. Based on NDA 202860 resubmission dated July 23, 2018, Vero Biotech (formerly known as GeNO, LLC), has sought U.S. marketing approval for the drug-device combination product, GēNOsyl (b) (4), in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The Listed Drug (LD) for this resubmitted NDA is INOmax (nitric oxide for inhalation) approved under NDA 020845. Vero Biotech’s drug-device combination will deliver the same concentration of NO for inhalation as the currently approved. INOmax® device. To support this application, Vero Biotech is relying on: a) information in the approved labeling for INOmax regarding the safety and efficacy of inhaled NO, b) clinical studies (in adults) conducted by Vero Biotech, c) (b) (4) and d) information in the public domain (i.e., published clinical studies on the safety and efficacy of inhaled NO).

III. Summary of Quality Assessments

The proposed GēNOsyl (b) (4) Delivery System® (GēNOsyl (b) (4)), a liquid-based delivery system for inhaled nitric oxide (NO), is proposed for the treatment of persistent pulmonary hypertension of the newborn. Orphan-drug designation for this indication was granted by the Agency under Orphan Designation 12-3685. The originally proposed drug-device combination product for inhaled NO i.e., the GeNOsyl MVG 2000 Delivery System has undergone significant design changes since the original NDA submission. The GēNOsyl (b) (4) proposed in the NDA resubmission, represents a significantly improved system with marked design changes aimed to consistently deliver a well-controlled levels of nitric oxide (NO) to the patients while restricting nitrogen dioxide (NO₂) levels within the safe limits. Prior to reaching the patient, the gas passes through an inline mixing chamber that is used to ensure a uniform intrabreath NO dose. Specifically, the GēNOsyl (b) (4) is designed to inject a constant flow of NO gas into the inspiratory limb of the ventilator circuit to deliver a constant concentration of NO to the patient. The

applicant contends that the GēNOsyl (b) (4) provides continuous integrated monitoring of inspired oxygen, NO and NO₂ concentrations, and a comprehensive alarm system.

The CMC deficiencies listed in the previously issued Complete Response Letter have been either addressed in this resubmission by providing the necessary data or their relevance has been obviated due to marked redesigning of the drug-device combination product. However, during a recent inspection of the Vero Biotech manufacturing facility (FEI: 3014617112) for this NDA, our field investigators identified a series of deficiencies, which were conveyed to the representative of the facility. The manufacturing site was deemed to be not ready for commercial manufacturing of the proposed drug-device combination product due to unresolved Form 483-listed deficiencies. Further, it is noted that determining the suitability of GēNOsyl (b) (4) for the production and consistent and safe delivery of NO drug product to the patient involves an evaluation of closely intertwined CMC, device and human interface-related details. While the OPQ Integrated Quality Assessment primary focuses on evaluation of CMC aspects, including the product quality and manufacturing considerations, we refer to CDRH and DMEPA reviews for evaluation of the device engineering, and device and human factor validation related studies.

A. Drug Substance Quality Summary

Nitric oxide (NO) drug substance, a colorless and odorless gas, is generated at the point-of-use within the GēNOsyl (b) (4). The drug substance has been well characterized using appropriate analytical tools such as (b) (4)

Nitric oxide (NO) drug substance quality is controlled by adequate in-process controls and release specifications, (b) (4)

(b) (4) The identity, quality and purity of each batch of N₂O₄ and antioxidant cartridges are assessed and confirmed according to the specifications using validated analytical procedures. Nitrogen dioxide (NO₂) is the only potential related impurity observed and monitored in the NO manufactured by the GēNOsyl (b) (4). An antioxidant cartridge is approximately 3.7 inches long with an outside diameter of 1.5 inches and an internal diameter of 0.25 inches with a tapered end. The cartridge (b) (4)

(b) (4) antioxidant cartridge release specification with well-justified acceptable limits of less than 2 ppm, which is within the safe limits for NO₂. The GēNOsyl (b) (4) system shutdown condition for NO₂ is 3 ppm. The NO₂ output above 2 ppm during the timeframe of the test indicates a cartridge NO₂ conversion performance failure.

Based on stability data, a (b) (4) retest period is acceptable for the N₂O₄ (b) (4) (b) (4) the current level of understanding is adequate to support the use of the cartridges as per the proposed specification for up to 12 months from their time of manufacture. The applicant has proposed the breakthrough testing (i.e., demonstration that the cassette excess capacity to convert the maximum level of NO₂ produced (b) (4) of N₂O₄ into NO) as the stability-indicating method of choice. This approach is acceptable; however, the applicant has not established a hold-time for the cartridges used in the manufacture of the cassettes.

B. Drug Product Quality Summary

The drug product is composed of (b) (4) ppm to 800 ppm nitric oxide (NO) in (b) (4) room air to be delivered at a recommended maximum dose concentration of 20 ppm to the patient to reduce the need for extracorporeal membrane oxygenation in near-term (>34 weeks gestation) or full-term neonates. There are no excipients added to the NO (b) (4) drug product after the generation of NO. Specifically, the GēNOsyl (b) (4) consists of two main subsystems; the nitric oxide drug product cassette and the console. The drug product cassette contains all components and material necessary to safely generate nitric oxide (NO) for inhalation. The console provides the NO delivery controls in addition to safety controls. The system operation involves continuous monitoring by electrochemical NO, NO₂, and O₂ sensors during use. The delivered NO concentration is regulated by the liquid vessel temperature and the console internal flow controls.

The finished nitric oxide drug product quality is controlled by adequate in-process manufacturing controls and quality control specifications using validated analytical procedures. All specifications for cassette testing are adequately justified. Validation information demonstrating that the analytical procedures used to test drug product are suitable for their intended purpose is adequate. The cassette is demonstrated to (b) (4) the capacity to convert maximum contained N₂O₄ into NO while maintaining the NO₂ levels below 2 ppm. A critical aspect of the design is that if functional defect is detected by the console during operation, there is a backup system in standby state, which is ready to provide nearly continuous NO supply with minimal interruption. The production of quality drug product has been verified by testing and comparison to acceptable reference standards. From analytical perspective, the chemiluminescence sensor is specific for NO. (b) (4) methodology for detection of NO₂ is highly sensitive and specific even in the presence of significant levels of NO. The proposed (b) (4) (b) (4) which is a simulated version of the commercial console under conditions that simulate proposed use, is acceptable. Based on data provided, the cassettes can typically provide NO at 20 ppm for a period of at least 24 hours without breakthrough NO₂ when the standard 20 ppm NO settings are in place. Various product development studies conducted by the applicant have shown that: a) NO gas, generated from liquid N₂O₄, is indistinguishable from a NIST traceable NO calibration gas standard, b) NO₂ conversion to NO from liquid N₂O₄ and from a calibrated cylinder produce chemically identical NO, and c) the GēNOsyl (b) (4), using a liquid N₂O₄ source material, is capable of delivering NO gas at a controlled target dose level. The product release specification includes testing for levels of NO₂ output with an acceptance limit of 2 ppm. Based on testing and risk assessment of product elemental impurities per ICH Q3D, the elemental impurity levels are below the control threshold (30% of the PDE) and no additional controls are necessary.

Manufacturing: The GēNOsyl (b) (4) operates by producing nitric oxide (NO) from N₂O₄ liquid, which is stored in a nitric oxide drug product cassette containing two antioxidant cartridges. (b) (4)



Container-Closure System: The proposed container closure system for the GēNOsyl (b) (4) drug product cassette houses the subcomponents necessary for the generation of GēNOsyl (b) (4) nitric oxide drug product. Based on appropriate testing, the applicant has demonstrated the adequacy of the proposed container closure system, including the primary and secondary packaging for the cassette.

Biocompatibility: The GēNOsyl (b) (4) is a liquid based NO delivery system for the administration of inhaled NO using a mechanical or manual ventilator. The device components evaluated for biocompatibility are part of the gas pathway, which delivers a constant intra-breath concentration of therapeutic NO to patients who are on a ventilator. No part of the device or supplied accessory components makes direct contact with the patient during use. The patient gas flow path includes flow through the cassette, console, and supplied ventilator circuit accessories. Leachable and extractable gas pathway material characterization performed on all GēNOsyl (b) (4) gas pathway component materials are adequate. A gas pathway evaluation for NO within the cassette and console has been carried out in accordance with ISO (b) (4) for emissions of Volatile Organic Compounds (VOCs) and particulate matter. Specifically, the risk assessment has focused on volatile compounds and particulates that may be released into the gas pathway of the GēNOsyl (b) (4) and, therefore, subject to inhalation by a patient. The VOCs identified in the gas pathway analysis, expressed as estimated daily intake, have been found to be at levels

below the established Toxicological Threshold of Concern (TTC). The particulate matter levels have not exceeded the allowable limits. Although no VOC exceeded a TTC (per ISO (b) (4) guidance), (b) (4) have been subjected to a more in-depth assessment because of the well-known toxicity limits for these chemicals. The potential levels of exposure for both (b) (4) have been demonstrated to be below toxicological thresholds of concern.

Stability, and Expiration Date:

(b) (4)

Thus, the proposed expiration dating period of 12 months appears to be reasonable. However, it is recommended that the 12-month expiration date be marked based on the manufacturing date of the oldest cartridge used to assemble the cassette, as opposed to the manufacturing date of the cassette. (b) (4)

IV. Assessment of Manufacturing Facilities

Given the significant changes made in product manufacturing and design of device components, new manufacturing facilities have been listed in the NDA resubmission. The listed manufacturing site i.e., Vero Biotech facility (FEI: 3014617112) performs product manufacturing, packaging, release and stability testing. Based on the initial risk assessment, this facility was deemed 'high risk' due to: a) lack of any prior FDA inspection record, b) high risk API (b) (4) c) product and device complexity (combination product designation). Because of a pre-approval inspection (PAI) of Vero Biotech manufacturing facility (FEI: 3014617112), a series of the FDA Form 483-listed deficiencies have been identified. Based on review of facility inspection results, and firm's response, it has been concluded that the manufacturing site is not ready for commercial manufacturing of the proposed drug-device combination product. As a result, the office of Process and Facilities has issued a 'withhold' recommendation for the facility. The (b) (4) facility, which performs (b) (4) was assessed during a (b) (4) surveillance inspection. The investigator's classification for this facility is VAI (voluntary action indicated), indicating that the facility is in a minimally acceptable state of compliance with regard to the current good manufacturing practice (CGMP).

V. Environmental Assessment

The applicant's requests for a categorical exclusion pursuant to 21 CFR 25.15(d) and 21 CFR 25.20 as described under 21 CFR 25.31(a) is acceptable.

VI. Labeling

Not applicable at this stage due to Complete Response recommendation made from CMC perspective.

VII. List of Deficiencies to be Communicated via the Complete Response Letter:

1. Manufacturing Facility Inspection

During a recent inspection of the Vero Biotech manufacturing facility (FEI: 3014617112) for this NDA, our field investigators conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this NDA is considered for approval.

2. Determination of Product Expiration Date

Regarding the stability studies, we note that a hold-time for the antioxidant cartridges used in the manufacture of the cassettes has not been adequately established. Based on your submitted stability data, the proposed expiration dating of 12 months for the GēNOsyl ^{(b) (4)} drug product cassette is acceptable. However, the date of expiration needs to be marked based on the date of manufacture of the oldest cartridge used in the cassette assembly, as opposed to the manufacturing date of the cassette.

VIII. Life Cycle Knowledge Management/Final Risk Assessment

Pleased view the following page:

Final Risk Assessment

NDA 202860 Resubmission (GēNOsyl (b) (4))

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors Affecting CQA	Initial Risk Ranking	Risk Mitigation	Final Risk Evaluation	Life Cycle Management Comments
Nitrogen Dioxide (NO ₂) Output (Impurity Content)	Manufacturing Controls Process Parameters Device Controls Cartridge Performance	H (High)	The product release specification includes testing for levels of NO ₂ output with an acceptance limit of < 2 ppm, which is within the permitted safety limits for this poisonous gas.	Acceptable	Any change in drug product release specification and/or changes in cartridges design needs to be carefully examined to ensure that final NO ₂ output levels are maintained at < 2 ppm.
Assay (API), Product Stability	Formulation Container Closure Process Parameters Device components	M (Moderate)	Based on the stability data, the proposed expiration dating of 12 months for the GēNOsyl (b) (4) drug product cassette is acceptable.	Acceptable	Any extension of expiration dating period needs to be carefully evaluated because the current stability data indicate that 12 months may be near the performance limit for the current cartridge design.
Manufacturing Controls	Process Parameters In Process Controls Product Device Functional Integration Manufacturing Practices cGMP Device Testing	H (High)	The product quality seems to be well controlled based on proposed manufacturing in-process controls and release specifications. However, the field investigators have identified a series of currently unresolved Form 483-listed deficiencies for the Vero Biotech manufacturing facility.	Not acceptable, and hence basis for a Complete Response recommendation.	Satisfactory resolution of Form 483-listed deficiencies is required.
Leak Test Pouch Seal Integrity	Cartridge Pressure (b) (4) Specification Container Closure Integrity	M (Moderate)	Controls for cassette assembly include adequate in-process controls such as (b) (4) (b) (4) Pouch seal integrity integrity test are adequate.	Acceptable	

Final Risk Assessment (continued)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors Affecting CQA	Initial Risk Ranking	Risk Mitigation	Final Risk Evaluation	Comments
Compatibility	Formulation Raw materials Process parameters Container Closure	L (Low)	Compatibility test studies are adequate.	Acceptable	
Uniformity of Delivered Dose Under Conditions of Use	Manufacturing Chemistry Console performance Cartridge Performance Device Controls	H (High)	Adequately ensured by the proposed drug-device product	Acceptable	All future modifications should be assessed while being mindful of the criticality of the cartridge design, manufacturing process parameters and device controls, including the alarm.
Particulate Matter	Formulation Container Closure Process Parameters Device controls	L (Low)	The particulate matter levels have not exceeded the allowable limits.	Acceptable	
Leachable Extracts	Container Closure Folds Creases, Tears	L (Low)	Leachable and extractable gas pathway material characterization performed on all GēNOsyl ^{(b) (4)} gas pathway component materials are adequate.	Acceptable	
Monitoring of NO, NO2	Drug-Device controls	H (High)	The system has continuous monitoring by electrochemical NO, NO2, and O2 sensors during use.	Acceptable	Any drug-device design changes will require careful evaluation to ensure continuous monitoring of NO, NO2, and O2

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 202860 resubmission (GēNOsyl ^{(b) (4)}) is not recommended for approval because the Office of Process and Facilities has issued a “Withhold” recommendation for Vero Biotech manufacturing facility (FEI: 3014617112). Satisfactory resolution of all the Form 483-listed deficiencies concerning this facility is required before this NDA is considered for approval.

Mohan Sapru, M.S., Ph.D.
Application Technical Lead (ATL)
CMC Lead for Cardiovascular and Renal Products
ONDP/DNDPI/NDPBI

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MOHAN K SAPRU
12/18/2019 04:31:38 PM



Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

ICC1900650 – Device Consult
ICCR CASE# 00011973
NDA 202860

Date: November 12, 2019
To: Brian Proctor (CDER/OND/ODEI/DCRP)
From: Neel Patel (CDRH/OHT1/DHT1C)

Through: Todd Courtney, Assistant Director (CDRH/ OHT1/DHT1C)

Applicant: Vero Biotech
Device: GēNOsyl (b) (4) Delivery System
Drug: GēNOsy (nitric oxide for inhalation)

I. Executive Summary

The Center for Drug Evaluation and Research (CDER) has requested CDRH consult review of the GēNOsyl (b) (4) Delivery System intended for delivery of nitric oxide for inhalation to newborns with hypoxic respiratory failure. In a prior consultation (ICC1800619 - ICCR2018-03302) of submission documents submitted under NDA202860/0023 and /0032, CDRH recommended the sponsor provide additional information to address deficiencies identified with the closed-loop technology within the device, NO2 delivery shutdown, EMC, Electrical Safety, and user manual.

This consult provides review and recommendation based on the additional information provided in response to these deficiencies. Based on review of additional information provided by the sponsor, CDRH believes all device review concerns to be resolved.

Table with 2 columns and 2 rows. Header: Digital Signature Concurrence Table. Row 1: Reviewer Sign-Off. Row 2: Branch Chief Sign-Off.

II. Materials Reviewed:

ICC1900650

1. \\CDSESUB1\evsprod\NDA202860\0046\m2\23-qos\regional-information-final.pdf
2. Device related documents in the following location: \\CDSESUB1\evsprod\NDA202860\0042\m3\32-body-data\32r-reg-info
3. \\CDSESUB1\evsprod\NDA202860\0035\m1\us\111-info-amend\response-information-request-final.pdf
4. \\CDSESUB1\evsprod\NDA202860\0049\m1\us\114-labeling\114a-draft-label

ICC1800619

1. \\CDSESUB1\evsprod\NDA202860\0023\m2\23-qos\regional-information.pdf
2. Device related documents in the following location: \\CDSESUB1\evsprod\NDA202860\0023\m3\32-body-data\32r-reg-info
3. \\CDSESUB1\evsprod\NDA202860\0032\m1\us\12-cover-letter\cover-letter-11202018-advice-letter.pdf

III. CDRH Review Team

ICC1900650

Reviewer	Review Topics
Neel Patel (ODE/DAGRID/ANDB)	Lead Review, Software
Sandy Weininger (OSEL/DBP)	Electrical Safety, Closed Loop System
Jeffrey Silberberg (OSEL/DBP)	Electromagnetic Compatibility
Sidra Mirza (ODE/DAGRID/RPDB)	Labeling

ICC1800619

Reviewer	Review Topics
Neel Patel (ODE/DAGRID/ANDB)	Lead Review
Bifeng Qian (ODE/DAGRID/INCB)	Biocompatibility
Sandy Weininger (OSEL/DBP)	Electrical Safety
Jeffrey Silberberg (OSEL/DBP)	Electromagnetic Compatibility
Joseph Jorgens (OSEL/DBP)	Software
Clarence Murray (ODE/DAGRID/INCB)	Toxicology / E&L / RA
Bahram Parvinian (OSEL/DBP)	Closed Loop System
Sidra Mirza (ODE/DAGRID/RPDB)	Labeling

IV. Indications For Use (as provided by the sponsor)

The indications for use are as provided below. Revisions (i.e. additional text) made by the sponsor are highlighted):

GēNOsyl^{(b) (4)} generates and delivers NO for inhalation at the point of use. The concentration of NO, as set by the user, is monitored and adjusted to accurately dose the patient throughout an inspired breath. Only validated devices / components should be used with the GēNOsyl^{(b) (4)}.

The intended population for inhaled NO treatment is term and near-term neonates in neonatal intensive care units (NICUs). Refer to the GēNOsyl (nitric oxide) for inhalation drug label for more detailed information.

The GēNOsyl^{(b) (4)} is intended for use by healthcare professionals (HCPs) who are licensed and actively practicing pediatric and/or neonatal respiratory therapists (RTs) in the United States. These users are required to set up, administer inhaled nitric oxide and provide respiratory care

(including initiation and maintenance of mechanical ventilators) in the critically ill neonatal population.

The GēNOsyl (b) (4) starts with liquid N₂O₄/NO₂, which is then converted in a proprietary Cassette to NO. The GēNOsyl (b) (4) delivers NO into the ventilator stream, where the NO joins a stream of air or O₂ and is diluted to the prescribed concentration. A Mixer then provides adequate mixing of the two gas streams.

The NO concentration (dose) to be delivered to the patient is selected by the user, set and maintained independently by means of computer-controlled air pumps, Cassette heaters, and a feedback loop that measures the delivered NO concentration.

The GēNOsyl (b) (4) takes a gas sample removed from the NO gas flow stream immediately prior to the patient and provides real-time output of the NO, NO₂, and O₂ concentrations that are being delivered to the patient. The continuous integrated gas monitoring includes a comprehensive alarm system.

The NO concentration detected from the sample line is used in a feedback loop to adjust the NO concentration delivered into the ventilator circuit.

The GēNOsyl (b) (4) includes a redundant Console for complete backup capability for delivery of NO for inhalation. Each Console has a back-up battery that provides up to 1 hour of NO delivery in the absence of an external power source.

ICC1800619 Reviewer Comment: There are no major concerns identified but it is noted that the IFU statement includes a large amount of descriptive information. However, exiting nitric oxide delivery systems (i.e. INOmax DS) also include a large amount of descriptive information in the IFU statement.

ICC1900650 Reviewer Comment: Upon request (Deficiency B6 below), the IFU statement was revised to state that “only validated devices/components should be used with the GeNOsyl (b) (4)”.

V. Device Description

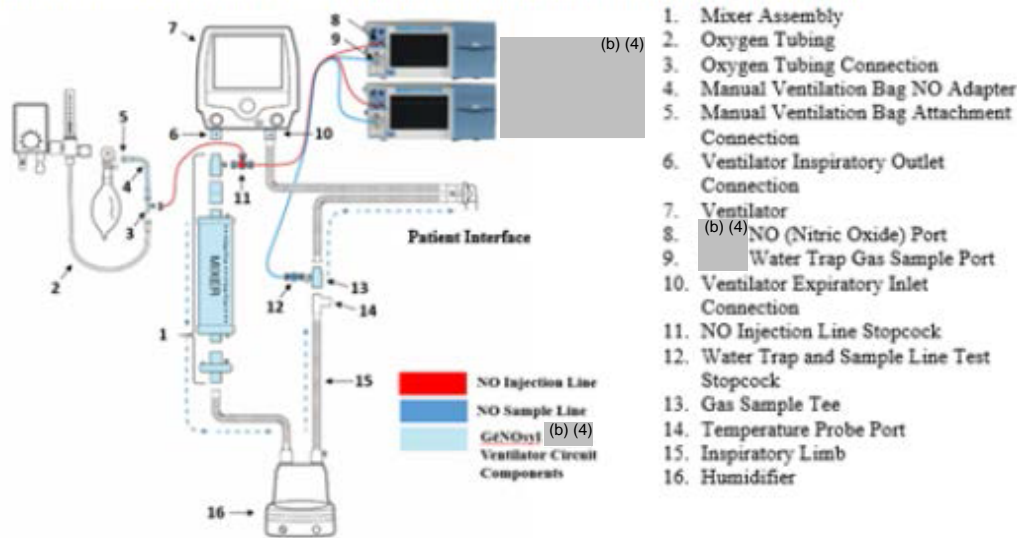
The GēNOsyl (b) (4) device continuously introduces a precisely-controlled concentration of nitric oxide (NO) into the inspiratory limb of the ventilator circuit. GēNOsyl (b) (4) utilizes the known properties of NO and other oxides of nitrogen, namely dinitrogen tetroxide (N₂O₄) and nitrogen dioxide (NO₂), to create a “tankless” drug/device combination product to produce, at the point of use, ultra-high purity NO for inhalation, providing a consistent, prescribed dose to the patient.

The GēNOsyl (b) (4) consists of two consoles each with its own independent cassette, the proper patient tubing lines to connect to the ventilator or external gas supply for a cannula, a supply line that connects both consoles to the patient line simultaneously, and a sample line that connects both consoles to the patient line simultaneously. Both consoles and associated equipment are mounted in a mobile cart. When used with a ventilator, the system also includes an inline mixer, which is used to ensure a uniform intrabreath NO dose.

Figure 1: GēNOsyl (b) (4)



Figure 2: GēNOsyl (b) (4) Configuration with Ventilator Circuit and Accessories



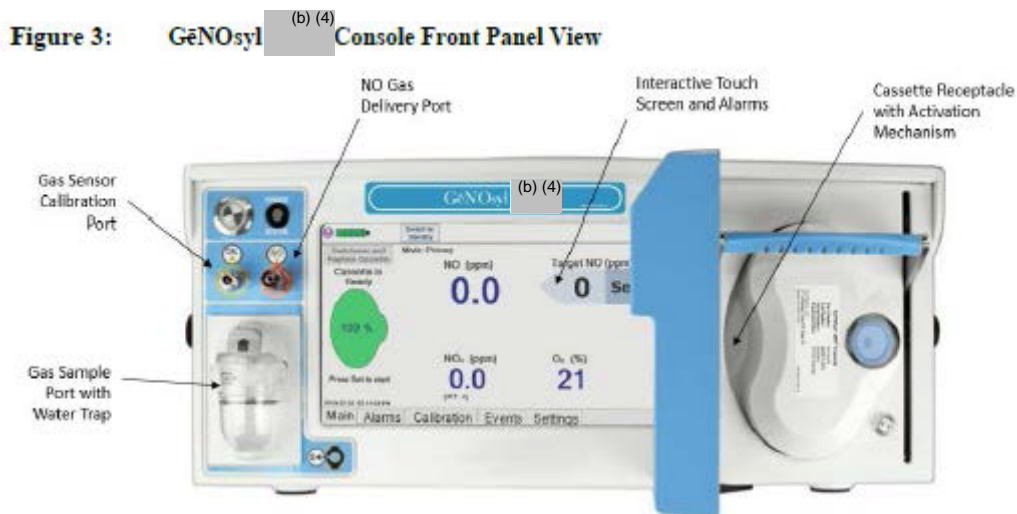
The system requires a GēNOsyl (b) (4) Console, a single GēNOsyl (b) (4) Cassette which contains liquid N₂O₄, and a pair of NO₂ to NO converting cartridges (antioxidant cartridges). Upon initiation of the system, the liquid N₂O₄ is heated and converts to NO₂ (gas) and N₂O₄ (gas) (b) (4). The NO₂ is then converted into NO using the Vero Biotech proprietary NO₂ to NO converting cartridges and delivered to the patient. The amount of NO presented to the patient is controlled by changing the temperature of the N₂O₄ Liquid Module to increase NO dose and by diverting excess NO supply away from the patient flow path and allowing the temperature of the N₂O₄ Liquid module to cool to decrease dose. The NO concentration is controlled via a feedback loop from a NO sensor, which monitors the NO in the patient line. The NO sensor output is compared to the demand NO concentration (NO concentration set point chosen by the user) by the control circuitry which in turn adjusts the liquid module temperature and flow controllers to achieve the target dose in the sample delivered to the patient.

The GēNOsyl^{(b) (4)} injects a constant flow of nitric oxide (NO) gas into the inspiratory limb of the ventilator circuit to deliver a constant concentration of NO to the patient. It provides continuous integrated monitoring of inspired oxygen, NO and nitrogen dioxide (NO₂) concentrations, and a comprehensive alarm system. Prior to reaching the patient, the gas passes through an inline mixing chamber which is used to ensure a uniform intrabreath NO dose.

ICC1800619 Reviewer Comment: The device is a nitric oxide delivery system intended for use in neonates for treatment of hypoxic respiratory failure. Unlike existing nitric oxide delivery systems (NODS) which use tanked nitric oxide gas for inhalation, the GēNOsyl^{(b) (4)} Delivery System^{(b) (4)} delivers nitric oxide for inhalation which is created at point-of-care with liquid N₂O₄ stored in a cassette^{(b) (4)}. The liquid N₂O₄, when heated, vaporizes and provides 2 molecules of NO₂. NO₂ is then converted to NO for delivery by passing through antioxidant cartridge.

Console and NO generation

The GēNOsyl^{(b) (4)} Console contains the electronics to control the production and to maintain the constant and precise delivery of NO.



The Console has a single Cassette containing liquid N₂O₄/NO₂ inside a stainless steel vessel (the liquid module) and proprietary conversion units. Upon initiation of the Cassette, the liquid N₂O₄ is heated, producing NO₂ gas, which is mixed with 0.6 LPM ambient air supplied by the Console. The NO₂/air is injected into the Cassette, which converts NO₂ to NO as the gas passes through the antioxidant cartridges inside the cassette. The Cassette is designed to provide NO in concentrations up to 80 ppm.

Cassette

The GēNOsyl^{(b) (4)} Cassette is a single use disposable component which contains the drug substance^{(b) (4)} liquid N₂O₄. The Cassette contains^{(b) (4)} the liquid N₂O₄ which is activated^{(b) (4)} inside a reaction vessel container when the cassette use is initiated. The reaction vessel is heated which pressurizes the liquid N₂O₄ contents, creating NO₂ gas. The NO₂ gas exits the reaction vessel and passes through a short length (about 1 inch) of small inner diameter gas chromatography capillary tubing, which regulates the NO₂ output rate of the liquid vessel. The heating temperature of the reaction vessel is controlled by the console to achieve the required NO₂ gas output rate from the liquid vessel. After exiting the liquid vessel, NO₂ gas is mixed^{(b) (4)} in the console at 0.6 LPM. The NO₂ in air^{(b) (4)} is advanced through a pair of cartridges which convert the NO₂ to NO in air which is delivered via the console to the ventilator circuit via the in-line mixing chamber

Figure 12: Cassette: Self-Contained Disposable Components with Inerting Viewing Window

(b) (4)



Feedback System (Closed Loop)

The system uses the NO concentration sampled from the ventilator circuit as the input for a constant system dose control.

NO Injection into the Ventilator Circuit.

After NO is produced in the Cassette, the NO injector introduces the concentrated NO into the ventilator circuit where the NO is diluted to the prescribed concentration (dose) and mixed with the O₂ or air supplied to the patient. Before the gas mixture reaches the patient, a sampling line directs a gas back to the Console, where gas sensors continuously measure the supplied NO, NO₂ and O₂. The Console software then compares the measured NO concentration to the set NO concentration and continuously adjusts delivery of NO to maintain the prescribed NO concentration (dose) delivered to the patient.

Mixer.

An inline Mixer is used in the ventilator circuit after the NO injection site and before the gas sampling site to thoroughly mix NO from the Console with the gas supplied by the ventilator to provide a uniform intra-breath NO delivery concentration.

Gas Monitoring.

The gas mixture delivered to the patient by the GēNOsyl (b) (4) is continuously monitored with two NO detectors, with one providing redundant back-up, as well as a detector for NO2 and O2. A sample of inspired gas is taken from the inspiratory limb, close to the patient, and is measured by the gas sensor within the Console. The gas monitoring sensors are electrochemical; they are specific to each gas and provide an electronic signal that is proportional to the concentration of gas present.

Alarms and Shutdown Safeguards.

The GēNOsyl (b) (4) alerts the user in the event of excursions of NO, NO2, and Oxygen from their expected ranges.

ICC1800619 Reviewer Comment: The system is designed to shut down NO delivery if NO exceeds 100 ppm and if NO2 exceeds 3 ppm.

Back-up NO Delivery

The Console that is not actively being used to administer NO serves as a Standby Console with a second Cassette loaded, but is not activated. If the Primary Console fails to deliver NO, the Back-Up Console is activated to continue NO delivery.

Transition to a new Cassette.

When a Cassette approaches depletion, the active/original Primary Console notifies the user to begin the transition to a new Cassette in the Standby Console. During the transition to a new Cassette, the target NO concentration is maintained by the two systems. The original Primary Console decreases the proportion of NO delivered in a controlled manner while the new Primary (previous Standby) Console delivers the remaining NO required to maintain the target dose. When the transition is complete, the new Primary Console / Cassette delivers the entire dose and the depleted Cassette is removed from the previous (original) Primary Console and now becomes the Standby Console. A new Cassette is inserted in the original Console, which is maintained in Standby mode for backup or transition as needed

Accessories

The following are used and supplied with the device:

PART	PART NAME	Part Number	Supplier
	Mixer (b) (4)	(b) (4)	Vero Biotech
	Adapter (b) (4)	(b) (4)	(b) (4)

Dose Range	1 to 80 ppm
Flow rate (max)	600 ml/min

ICC1800619 Reviewer Comment: The NO delivery accuracy specification (b) (4).

Gas Measurement

Gas	Range	Resolution	Accuracy
NO	0-10 ppm	0.1 ppm	≤20ppm: +/- (20% of actual concentration + 0.5 ppm) >20ppm: +/- (10% of actual concentration + 0.5 ppm)
	10-100	1 ppm	
NO ₂	0.0 – 12 ppm	0.1 ppm	+/- (20% of actual concentration + 0.5 ppm)
O ₂	18- 100%	1%	+/- volume fraction of 2.5% +2.5% of gas level

ICC1800619 Reviewer Comment: The gas measurement accuracy (b) (4).

VI. Labeling

The submission provides a user manual for the (b) (4) as well as device labels for the console, cassette, mixer, gas lines, cart, and ventilation bag adapter. The device labels are acceptable and the user manual provides acceptable instructions for use.

In review of the user manual, the consulting reviewers Sidra Mirza and Jeffrey Silberberg identify minor concerns which should be addressed. Please see the Deficiencies section below and their consulting reviews for additional detail. The concerns identified were provided to the sponsor in a General Advice Letter dated November 16, 2018. In a response dated November 19, 2018, the sponsor noted that the requested changes will be made and provided in a revised user manual.

ICC1900650 Reviewer Comment: All remaining concerns with the user manual were adequately addressed.

VII. (b) (4) Shelf Life



The Cassette shelf life is determined through drug product stability testing performed as presented in section 3.2.P.8 Stability. (b) (4)

(b) (4)

ICC1800619 Reviewer Comment: Review of the drug product stability is deferred to CDER/OPQ.

VIII. Biocompatibility

The GēNOsyl^{(b) (4)} system is considered a gas pathway medical device with no direct patient contact. According, the applicable biological safety testing was determined according to ISO ^{(b) (4)} *Biocompatibility evaluation of breathing gas pathways in healthcare applications – Part 1: Evaluation and testing within a risk management process. The patient gas flow path includes flow through the cassette, console, and supplied ventilator circuit accessories. The complete list of patient gas flow contacting materials supplied by Vero Biotech is presented in Exhibit 6-F (of the submission).*

(b) (4)

ICC1800619 Reviewer Comment: Review of the biocompatibility of the device is provided by consulting reviewers Clarence Murray and Bifeng Qian. This does not include the drug cassette, which is considered part of the container closure and deferred to CDER/CMC.

Dr. Murray provided review of the toxicological risk assessment for the (b) (4) gas pathway. He notes the VOC and particulate matter testing conducted provide adequate results and were tested appropriately for the neonate population.

Dr. Qian provided review of materials in the humidified gas pathway. In her initial review, she noted concern with the sponsor's evaluation and noted the sponsor did not provide any biocompatibility endpoints assessments for the humidified gas pathway contacting devices or accessories or explain why the biocompatibility assessments are not necessary. The concern was provided to the sponsor in a General Advice Letter dated November 16, 2018. In a response dated November 19, 2018, the sponsor provided additional information adequately addressing the concern. The sponsor clarified:

- The complete list of all devices and accessories that will be used for delivery of nitric oxide for inhalation along with their regulatory status and patient contact types are identified.



- No device or accessory supplied by Vero Biotech makes direct contact with patients.

For additional detail please see the consulting memos.

IX. Software

The sponsor has provided software documentation for a major level of concern as recommended by the FDA Guidance, "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices". The documentation is reviewed by consulting reviewer, Joseph Jorgens. He notes the submission provides acceptable software documentation as follows:

1. Level Of Concern: Acceptable

In (b) (4) Section 7.3 entitled Level Of Concern the firm provided the correct determination of the Level Of Concern and included their supporting rationale: MAJOR.

2. Software Description: Acceptable

In (b) (4) Section 7.2 entitled Software Description the firm provided an acceptable overview of the device features that are controlled by software, and a description of the intended operational environment, which included information on the programming language and the hardware platform.

3. Device (including software) Hazard Analysis: Acceptable

In (b) (4) Section 7.6.2 entitled Risk Management, in Exhibit 10A4 entitled Hazard Analysis and in Exhibit 10A6 entitled Software FMEA the firm provided an acceptable description of the hazards (including clinical hazards) presented by this device, the causes and severity of the hazards, the method of control of the hazards and the testing done to verify the correct implementation of that method of control, and any residual hazards.

4. Software Requirements Specifications (SRS): Acceptable

In (b) (4) Section 7.5 entitled Software Requirement Specification and in Exhibits (b) (4) Software Requirement Specification the firm provided acceptable Software Requirements Specifications, which documented the functional, performance, interface, design and development requirements.

5. Architecture Design Chart: Acceptable

In Exhibit 7C1 entitled Software System Architecture the firm provided an acceptable detailed depiction of functional units and software modules, which included state diagrams as well as flow charts.

6. Software Design Specification (SDS): Acceptable

In (b) (4) Section 7.6 entitled Software Design and in Exhibits 7D1 – 7D7 the firm provided acceptable Software Design Specification which describes how the requirements in the Software Requirements Specifications (SRS) are implemented.

7. Traceability: Acceptable

In (b) (4) Section 7.8 entitled Software Traceability Analysis and in Exhibit 7E1 entitled Software Traceability Matrix the firm provided acceptable traceability, which provides traceability among identified clinical hazards and mitigations, requirements, specifications, and verification and validation testing.

8. Software Development Environment Description: Acceptable

In (b) (4) Section 7.4 entitled Software Development Environment Description the firm provided an acceptable description of the software development environment, (b) (4)

9. Verification and Validation Documentation: Acceptable

In (b) (4) Section 7.7 entitled Software V and V and in Exhibits 7F15 – 7F27 the firm provided acceptable unit, integration and system level test protocols, including pass/fail criteria, test reports, summaries and tests results.

10. Revision Level History: Acceptable

In (b) (4) Section 7.10 entitled Revision Level History the firm provided an acceptable revision history log documenting all major changes to the software during its development cycle and the release version numbers.

11. Unresolved Anomalies (bugs): Acceptable

In IND-Response (b) (4) in Section 7.12 entitled Unresolved Anomalies the firm provided an acceptable list of the remaining software anomalies, annotated with an explanation of the impact of the anomaly on safety or effectiveness, including operator usage and human factors.

ICC1900650 Reviewer Comment: In the additional information provided in the resubmission dated June 21, 2019, the sponsor reported modifications made to the software to address all unresolved anomalies. No concerns are identified in review of the identified list of updates.

12. Cyber and Information Security: N/A

13. Run-Time Error Detection: Acceptable

In (b) (4) Section 7.7 entitled Software V and V and in Exhibit 7F27 entitled Software Static Analysis Report the firm provided an acceptable description and discussion of how they address Run-Time errors.

X. EMC & Electrical Safety

The GēNOsyl (b) (4) complies with the applicable voluntary standards which include ANSI (b) (4) IEC 60601-1-2. (u) (4). The overall mechanical, electronic, and safety features of the GēNOsyl (u) (4) Delivery System comply with these voluntary standards including ANSI, (b) (4) ES 60601-1 for Electrical Safety and IEC 60601 (b) (4) for Electromagnetic Compatibility.

(b) (4)



Response Adequate: The response is reviewed by consulting reviewer, Jeffrey Silberberg. The sponsor agreed to the requested modification and provided a revised manual.

XIV. Recommendation

The sponsor has addressed all device concerns.

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/s/

BRIAN L PROCTOR
12/23/2019 12:48:28 PM

NDA/ANDA 202860

GeNOsyl™ MVG-2000 Delivery System

GeNO LLC

Charles F. Jewell Jr.
Division of Cardiovascular and Renal Drug Products

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1. NDA 202860
2. REVIEW #: 1
3. REVIEW DATE: 19-Apr-2013
4. REVIEWER: Charles F. Jewell Jr.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Meeting Minutes (by Russell Fortney - Discussion with applicant about RTF issues)	04-Sep-2012
Intercenter/Combination Products Consult (by Russell Fortney - CDRH New Delivery System Review)	17-Sep-2012
Intercenter/Combination Products Consult (by Teshara Bouie - CDRH Cartridge Manufacturing Sites)	15-Oct-2012
74-day Letter with CMC and Device Requests for Information.	11-Nov-2012
CMC Information Request/Comments on 74-day letter response	21-Feb-2013

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
NDA 202860SDN 1: New NDA	21-Mar-2012
NDA 202860 SDN 3 (Meeting/Meeting Request)	14-Jun-2012
NDA 202860 SDN 4 (Resubmission @ RTF)	30-Aug-2012
NDA 202860 SDN 5 (Labeling/SPL Draft)	05-Oct-2012
NDA 202860 SDN 8 (Quality/Device Info)	15-Nov-2012
NDA 202860 SDN 9 (Quality Response to IR)	30-Jan-2013

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: GeNO LLC
Address: 2941 Oxbow Circle
Cocoa FL 32926
Representative: David Fine, Ph.D., President
GeNO LLC
Telephone: 321-785-2601
E-mail: david.fine@genollc.com

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: GENOSYL(TM)
- b) Non-Proprietary Name (USAN): Nitric Oxide
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: Type 5 - New Formulation or New Manufacturer
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2); Listed Drug is NDA 20845 from INO; Name of Drug: INOmax; 800 ppm nitric oxide balance Nitrogen which is diluted and blended with air before delivery to patient using a specifically designed device.

10. PHARMACOL. CATEGORY: short term vasodilation of the cardiopulmonary vasculature

11. DOSAGE FORM: inhaled gas

12. STRENGTH/POTENCY: 0 - 20 ppm nitric oxide (b) (4)

13. ROUTE OF ADMINISTRATION: inhalation

Chemistry Review Data Sheet

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name: Nitric Oxide

Molecular Formula: NO

Molecular Weight: (b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Inadequate	1-Feb-2013	deficiencies communicated to DMF holder; loa: 18-Oct-2012

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
		(b) (4)
IND	109066	GeNO Nitrosyl Gas (NO ₂ (b) (4)) for treatment of PAH (b) (4) Submitted 29-Oct-2010 (Currently Active)
		(b) (4)
NDA	20845	INO Therapeutics, Inc.; INOmax (Reference Drug, nitric oxide 100 ppm and 800 ppm) in conjunction with ventilator support. Approved 23-Dec-1999

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	pending	3/20/2013	OC
Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	NA		
OPDRA	NA		
EA	adequate	3/20/2013	Charles Jewell
Microbiology	NA		

Chemistry Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
CDRH	(b) (4)	2/19/2013	Anh Nguyen
Office of Compliance	pending	3/20/2013	

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:

The Chemistry Review for NDA 202860

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is not recommended for approval from the Chemistry, Manufacturing and Controls perspective. (b) (4)

[Redacted]

The Establishment Evaluation System report from the Office of Compliance is also pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

[Redacted]

(b) (4)

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Executive Summary Section

(b) (4)

C. Basis for Approvability or Not-Approval Recommendation

We recommend a complete response

(b) (4)

A list of proposed complete response comments are included at the end of this review.

A list of proposed complete

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

Chemist Name/Date: Charles Jewell, 19-Apr-2013

Chemistry Team Leader Name/Date: Kasturi Srinivasachar, 19-Apr-2013

CMC Project Manager Name/Date: Teshara Bouie, 19-Apr-2013

OND Regulatory Project Manager Name/Date: Teshara Bouie, 19-Apr-2013

CMC Branch Chief / Secondary Reviewer Name/Date: Ramesh Sood, 19-Apr-2013

C. CC Block

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHARLES F JEWELL
04/19/2013

RAMESH K SOOD
04/19/2013